Case Report

# Composite Paraganglioma–Ganglioneuroma of the Urinary Bladder: A Clinicopathologic, Immunohistochemical, and Ultrastructural Study of a Case and Review of the Literature

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## Abstract

Urinary bladder paragangliomas are rare. An 81-yr-old woman was admitted because of whole-stream painless hematuria. Investigations revealed a pedunculated bladder tumor. Pathological examination showed a biphasic tumor, composite paraganglioma–ganglioneuroma. The two separate components were documented by both immunohistochemical and ultrastructural studies. A review of the English literature on urinary bladder paragangliomas showed that the present case is the first case with this unique feature documented in detail, and the patient is the oldest one being reported.

***Key Words:*** Bladder; paraganglioma; ganglioneuroma; composite.

## Introduction

Tumors arising from the neural crest in the adrenal medulla are known as pheochromocytoma, but those from the extraadrenal sites were termed paraganglioma. Paragangliomas in the urinary bladder are rare. Less than 200 cases have been reported in the English literature [1–128]. The first case was reported by Zimmerman et al. in 1953 [1]. Paraganglia of the urinary bladder are generally considered a precursor tissue of urinary bladder paraganglioma. It is assumed that the paraganglioma arises from small nests of paraganglionic tissue, which have persisted along the aortic axis and in the pelvic region, and these remnants of paraganglionic tissue migrate into the urinary bladder. Honma was the first person to examine the incidence of the normal paraganglia in the urinary bladder in 1993, and found the presence of paraganglionic tissue in 51.8% of the 409 urinary bladders collected at autopsy [129].

In this article, we present a unique case of composite paraganglioma–ganglioneuroma arising from the urinary bladder. The features are characterized and confirmed by immunohistochemical and ultrastructural studies. In addition, the literature on this rare entity is reviewed.

## Case Report

A 81-yr-old Chinese woman presented with whole-stream painless hematuria. There was no evidence of fever, loin pain, or other urinary symptoms. She had no previous record of hematuria, hypertension or other urinary symptoms. No family history of neurofibromatosis or other neurocutaneous phakomatoses was noted. On examination, she was afebrile, and the

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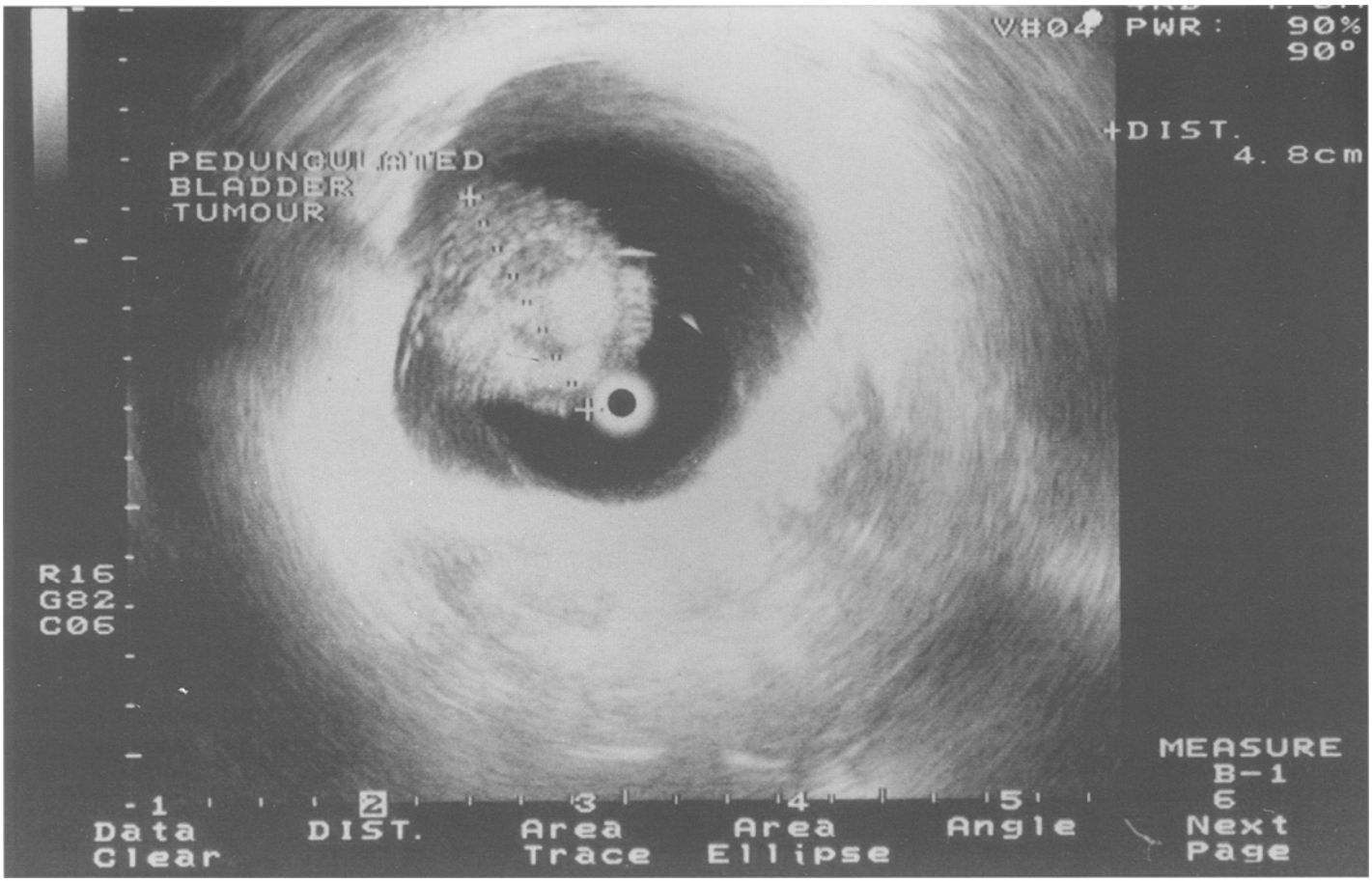



**Fig. 1.** Transurethral ultrasonogram showing a large pedunculated tumor at the right anterolateral wall of the bladder.

blood pressure was normal. There was mild tenderness in the suprapubic region.

Laboratory data of the patient after admission showed that blood counts and renal function were within the normal range. Bilateral apical fibrosis compatible with past history of tuberculosis was noted on the chest X-ray. The results of urine cytology and culture were unremarkable. Flexible and rigid cystoscopy showed that the bladder was full of blood clot and necrotic materials. Biopsy was taken and revealed mild cystitis. An intravenous urogram detected a large lucent filling defect in the right upper, outer quadrant of the urinary bladder. The flexible cystoscopy was then repeated and revealed a large pedunculated tumor on the right lateral wall of the urinary bladder. Transurethral ultrasonogram confirmed the presence of a pedunculated tumor, 4.8 cm in diameter, on the right anterolateral wall of the urinary bladder. The tumor had a narrow stalk and showed no evidence of muscle infiltration (Fig. 1). Transurethral resection of the bladder tumor was then performed. Follow-up cystoscopy and biopsy 3 mo after operation revealed no evidence of residual tumor.

Pathologic examination of the resected tumor showed fragments of tumor tissue with extensive areas of necrosis. The tumor had two components. In one portion of the tumor, tumor cells were polyhedral and arranged in nests (Fig. 2). They had basophilic granular cytoplasm and small hyperchromatic nuclei. Occasional eosinophilic hyaline globules were present. The features were those of a paraganglioma. The other

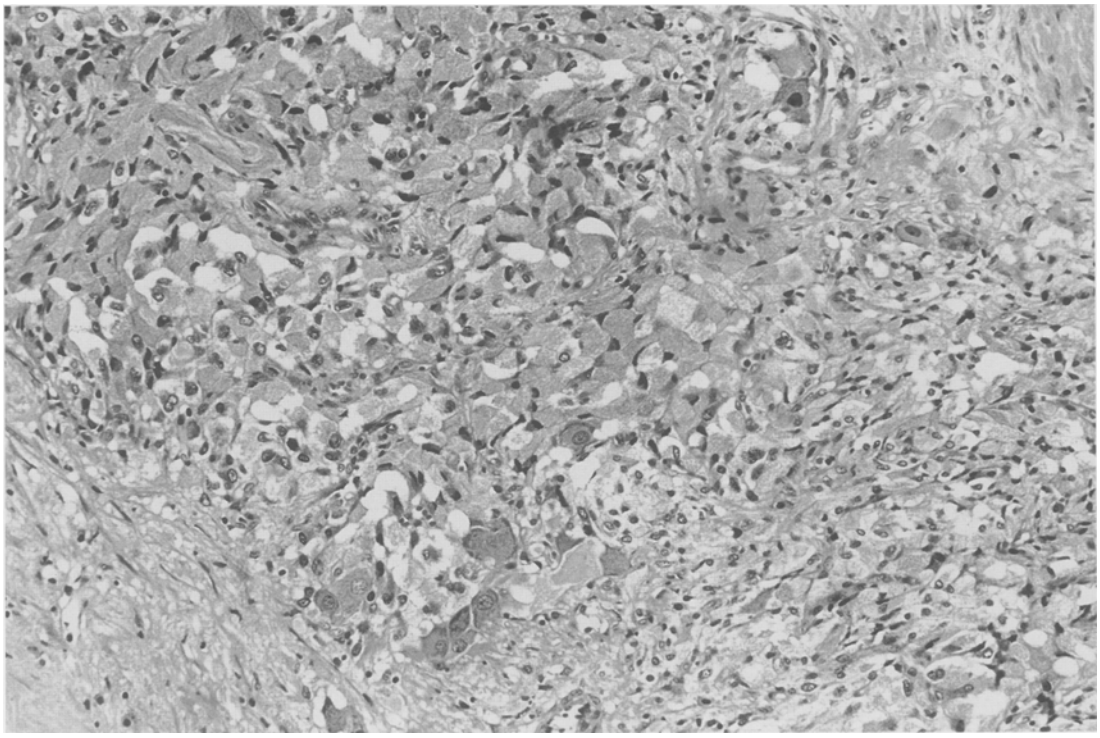


**Fig. 2.** Some areas of the tumor showing features of a paraganglioma. (H&E, original magnification ×480.)

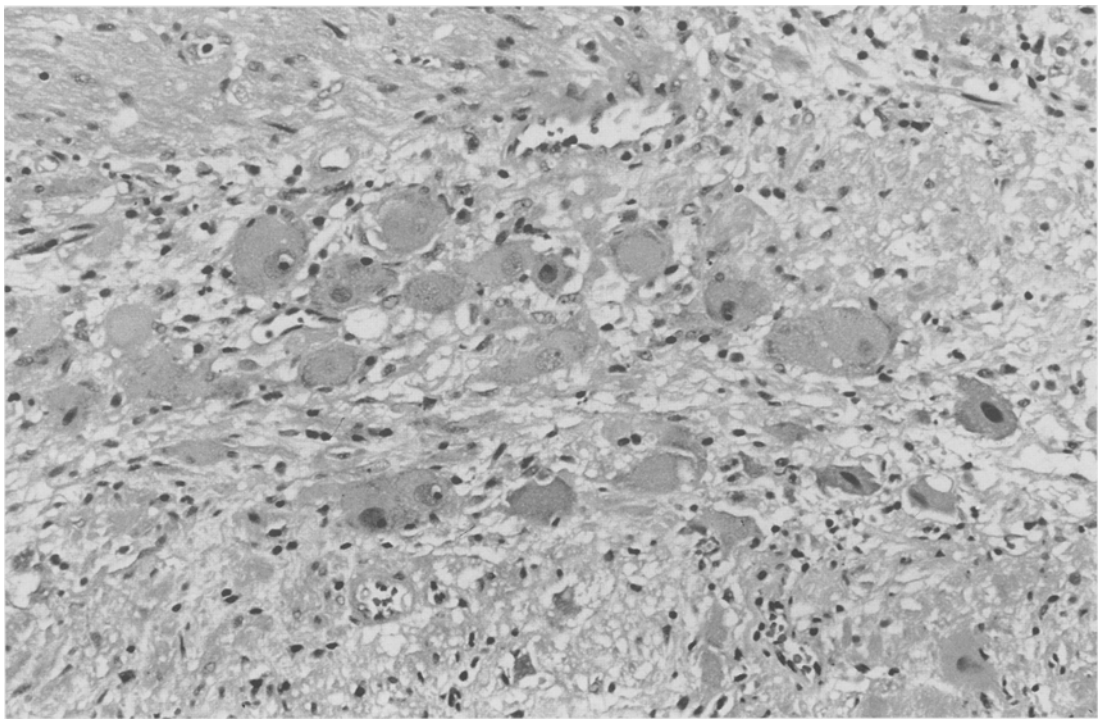


**Fig. 3.** Some areas of the tumor showing features of a ganglioneuroma. (H&E, original magnification ×480.)

part of the tumor consisted of tumor cells resembling ganglionic cells (Fig. 3). They had abundant eosinophilic cytoplasm with basophilic stipples and large, round nuclei with prominent nucleoli. Eosinophilic fibrillary stroma was present. The mor-

phologies of these were those of a ganglioneuroma. Focal interminglings of the two tumor parts were noted. Overall, the diagnosis was a composite paraganglioma–ganglioneuroma of the urinary bladder. Representative tissues were chosen for immunohistochemical and ultrastructural studies.

## Methods

Immunohistochemical study was conducted on 3-μ sections from representative blocks using the avidin–biotin–peroxidase complex method [130]. Appropriate negative (using buffer solution instead of primary antibodies) and positive controls from normal tissues were also examined. The antibodies to the following antigens were used: neuron-specific enolase (polyclonal; prediluted; Biogenex, CA, USA), synaptophysin (monoclonal; 1:10; Boehringer Mannheim Biochemica, Lauterstein, Germany), chromogranin (monoclonal; pre-diluted, Biogenex, San Ramon, CA), S-100 protein (polyclonal; 1:200; Dakopatts, Glostrup, Denmark), neurofilament (monoclonal; 1:10; Monosan, Uden, Netherlands), and Mak-6 (monoclonal; 1:2; Triton, CA). Antigen retrieval by microwave (at 95°C for 9 min) and trypsin (at pH 7.6 for 20 min) was done before application of some antibodies. Microwave incubation was done for synaptophysin and chromograninn, whereas trypsin was used for S-100, neurofilament, and Mak-6.

Tissue for ultrastructural examination was retrieved from the formalin-fixed, paraffin-embedded material. Briefly, the tissue was dewaxed, rehydrated in graded alcohols, and embedded in epoxy resin. Semithin sections (1-μ thick) were stained with toluidine blue and examined under light microscopy to confirm the areas of interest. Ultrathin (0.02-μ thick) sections were subsequently cut, stained with uranyl acetate and lead citrate, and examined with JEOL 100SX transmission electron microscope at 80 kV.

## Results

### Immunohistochemistry

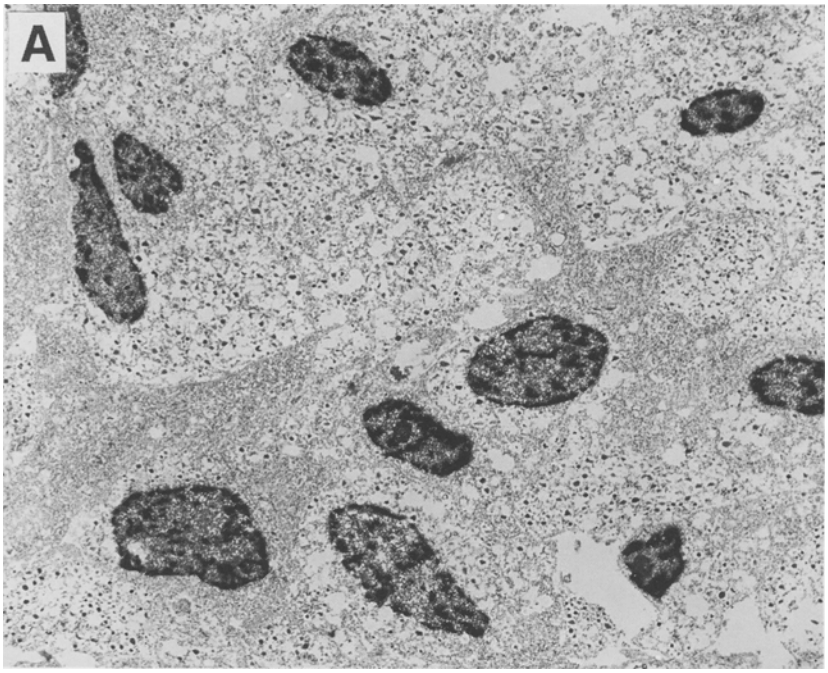
The basophilic tumor cells were positive for neuron-specific enolase, chromogranin, and synaptophysin, and negative for cytokeratin (Mak-6). Sustentacular cells were identified by S-100 protein. The ganglionic cells were also positive for S-100 protein, but the fibrillary matrix was positive for neurofilament.

### Electron Microscopy

Ultrastructural examination confirmed that the tumor was composed of different cellular components, which included neuroendocrine and ganglionic cells. The neuroendocrine cells were characterized by numerous electron-dense neurosecretory granules in the cytoplasm (Fig. 4). The ganglion cells showed peripherally situated nuclei possessing prominent nucleoli. The cytoplasm contained abundant organelles, including small stacks of rough endoplasmic reticulum, lysosomal granules, and scattered neurosecretory granules (Fig. 5).

## Discussion

The occurrence of both neuroendocrine and neural cells in the same tumor is not surprising when one recalls that neoplastic transformation occurred at the level of sympathogonia and was followed by a bidirectional maturation process to neuroblast and pheochromoblast. However, composite neruoendocrine–neural tumors are very rare. Approximately 30 cases were reported in the literature [131–134]. Many of these



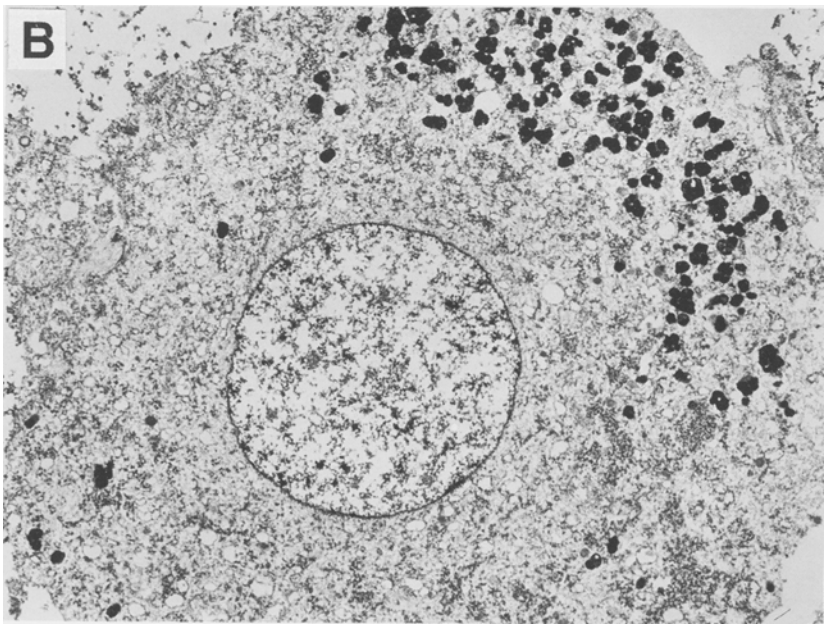




**Fig. 4. (A)** Electron micrograph of a clusters of neuroendocrine cells containing a large number of neurosecretory granules in their cytoplasm (original magnification ×3230). **(B)** High-power view of the tumor cells in A (original magnification ×8000).

cases were composite pheochromocytoma–ganglioneuromas noted in the adrenal glands. A few composite paraganglioma–ganglioneuromas were also reported in the retroperitoneum [132]. There was no formal description of a case in the urinary bladder in the English literature.

Leestma and Price mentioned a paraganglioma with large area resembling the pattern of ganglioneuroma in their analysis of 24 urinary bladder paragangliomas in 1971 [27]. In 1980, Hurwitz et al. reported, in a clinicopathologic conference, a bladder tumor in a 49-yr-old white woman [55]. They labeled it pheochromocytoma with interspersed large foci of ganglioneuroma. Overall, these cases lack in-depth documentation of clinicopathologic features. The current case is the first case of composite paraganglioma–ganglioneuroma having well-documented clinicopathologic features. The two separate components of the tumor were also confirmed by immunohistochemical and ultrastructural studies.

To date, 184 (including the present case) urinary bladder paragangliomas were reported in the English literature [1–128]. Although Honma found that parganglia of the bladder were more common in men [129], earlier reviews reported that urinary bladder paragangliomas occurred more commonly in women [69,77]. In this article on a larger number of reported cases, urinary bladder paragangliomas were noted in roughly the same frequency in women and men (male to female ratio = 0.9:1). The ages of these patients ranged from 10 to 81 yr (mean 39 yr). The current case is the oldest patient reported in the literature.

The tumor often presented with a classical triad of hematuria, hypertension, and "attacks" related to the release of tumorigenic amine during micturition. However, exceptions do occur. As illustrated in the present case, gross hematuria was the only presenting symptom. The diameter of these tumors ranged from 0.2 to 13 cm with a mean of 3.6 cm. Honma noted the paraganglia were present in any portion of the urinary bladder [129]. In concurrence

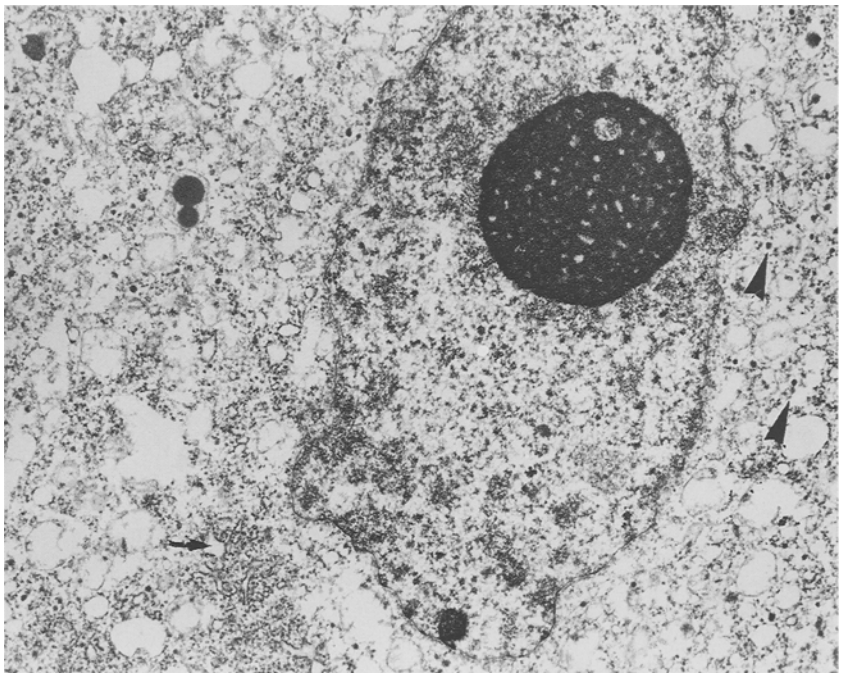


**Fig. 5.** Electron micrograph of a tumor cell showing ganglionic cell differentiation with small stacks of rough endoplasmic reticulum (arrow) and scattered neurosecretory granules (arrowheads). (Original magnification ×7280.)

with this finding, paragangliomas were seen in any portion of the urinary bladder: 12.5% in anterior wall, 9% in posterior wall, 25% in right lateral wall, 19.4% in left lateral wall, 12.5% in trigone, 6.3% in neck, and 15.3% in dome. Twenty-one percent of the reported cases were malignant.

Paraganglioma of the urinary bladder were documented in different populations. Of the 184 cases reported in the English literature, 6% ($n$ = 11) were reported in the Chinese populations [40,84,87,108,109]. The features of the cases reported in the Chinese were similar to those in the other populations. Four (including the current one) cases were reported in Hong Kong [40,108]. One of these cases showed a peculiar association with carcinoid [108]. Also, in our previous investigation, 9% of the paragangliomas was from the bladder [135].

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